Remarks

Applicants wish to thank Examiner Lin for the helpful interview with Applicant, Dr. Neal Gordon, and Applicants' representative, Edmund Pitcher, on Thursday, April 26, 2007. During the interview, various issues and options were discussed. Attorney Pitcher discussed at length his view that the outstanding obviousness rejections were improper under prevailing interpretations of 35 U.S.C. §103. Specifically, Attorney Pitcher indicated that the references identified by the Office did not disclose or suggest the subject matter claimed by Applicants, *taken as a whole,* but rather simply amounted to art teachings of some, but not all, of the claimed elements of Applicants' invention, that none of the references address or recognize the problems Applicants have solved, and that there was no reason apparent in the art or in the texts of the references suggesting that portions of their teaching should be combined.

As discussed in the interview, and as suggested by Examiner Lin, Applicants have amended claim 1 to place this application in condition for allowance. Attorney Pitcher respectfully requests that Examiner Lin call him (office 617-570-1780, cell 617-840-7767) if there are any unresolved issues which need to be addressed before mailing a Notice of Allowability or Notice of Allowance.

Claims 1 and 8 have been amended without any intention of disclaiming equivalents thereof. Upon entry of this paper, claims 1-10, 12-14, 16-20, 22-25, 31-35, 126, 127 and 129-132 will be under consideration, and claims 11, 15, 26-30, and 128 have been withdrawn from consideration by the Examiner. Claim 1 of the present invention has been amended to recite a method for detecting the presence and location of a post-translational modification (PTM) on a target protein within a sample. Support for this amendment appears throughout the application as filed, for example, on page 5, lines 23-26, and in claims 53 and 54 of the application as filed. In addition, claim 1 has been amended to incorporate the element of claim 21 to recite generating a capture agent that specifically binds said PET separate from said post-translational modification on said fragment. Support for this amendment appears throughout the application as filed, for example, in claim 21 and in Figures 22 and 23 as filed. Claim 21 has been cancelled. Claim 4 has been amended to include Nearest Neighbor amino acid analysis. Support for this

amendment appears throughout the application as filed, for example, in Figure 20 of the application as filed. Applicants have amended claims 8, 10 and 33 for clarity.

Rejection Under 35 U.S.C. § 103(a) over Katz in view of Gembitsky

Claims 1-3, 7-10, 12-14, 16-25, 31-35, 126, 127, 129 and 130-132 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over United States Patent Application Publication No. US 2002/0137119 by Katz ("Katz") in view of United States Patent Application Publication No. US 2005/0153298 by Gembitsky *et al.* ("Gembitsky"). Applicants respectfully request reconsideration and withdrawal of this rejection in view of the present amendments and following remarks.

The claimed subject matter of Applicants' application enables the measurement of the state of PTMs (of various kinds) of multiple proteins, in parallel, and *with positional detail within a protein.* Claim 1 of the present invention has been amended such that all claims are limited to a method for detecting the presence and location of a PTM on a target protein within a sample. Applicants respectfully submit that Katz and Gembitsky, alone or combination, fail to teach or suggest a method that detects the location of a PTM on a target protein or how this might be accomplished.

Katz provides a method for generating novel peptide antigens which when administered to an immunocompetent host are capable of effectively inducing the production of protein-specific antibodies which can be used to detect the protein in samples, which contain low protein concentrations and/or low exposure of protein-specific antigenic regions. Paragraph 59. With respect to PTMs, Katz indicates that preferred peptide products are those lacking any PTM sites, since PTM amino acid sequences are often difficult to purify, and are frequently poor immunogens. Paragraph 92. However, Katz does mention that peptide products which include PTM, which indicate a biological activity of the polypeptide-of-interest can also be used. Paragraph 93. As noted in the Office Action, Katz does not teach using a secondary capture agent for detection. Page 4, Paragraph 2. Rather, Katz describes labeling the examined polypeptide for direct detection or labeling a synthetic peptide and detecting the examined polypeptide via competitive binding. Paragraphs 43-44.

Gembitsky is directed to methods for using protein micro-arrays and/or multiplex coded microbeads in combination with multilayered affinity interaction detection (MAID) to permit high throughput analysis of cellular protein modifications and functional protein interactions. Generally, Gembitsky contemplates that an X number of detectably distinct affinity reagents, where X is an integer from 1 to N, can be used to detect an N number of post-translational modifications on a protein bound to a protein capture agent on a microarray. Paragraph 54. That is, Gembitsky describes detecting different types of PTMs on proteins. However, the only examples of PTMs in Gembitsky involve phosphorylation at Tyr residues using a p-Tyr detection antibody, although other types of PTMs are said to be detectable. Because many proteins have multiple pTyr (or other) modifications, the Gembitsky approach is *not specific to a given site*, and at best could indicate whether a given protein in a sample is modified or not. Gembitsky apparently does not recognize this as an issue, and mentions no modification to correct this drawback. Additionally, Gembitsky cannot detect modifications other than those accessible on a protein's surface. Buried modifications are invisible to Gembitsky.

Accordingly, neither Katz nor Gembitsky, alone or combination, teach or suggest a method that detects the location of a PTM on a target protein, as required in each and every claim of the present invention.

Second, claim 1 has been amended to incorporate the element of claim 21 to recite generating a capture agent that specifically binds a PET on a fragment separate from a PTM on the fragment. Applicants submit that neither Katz nor Gembitsky, alone or combination, teach or suggest this element of the present invention.

Specifically, as noted above, Katz describes using only a single capture agent, with direct or competitive detection of the peptide. Katz's peptides preferably lack post-translational modification sites, but the peptide products, preferably 5-12 amino acids in length, can include post-translational modification. Paragraphs 92-94. This means that, to detect PTMs, the Katz process requires generation of unique binding antibodies to each PTM in the assay. As the use of only a single capture agent and the preferred size of Katz's peptides indicate, a Katz antibody capture agent is generated against a peptide, not a part – a PET – on the peptide. Paragraphs 122-126 and Example 1, Step 5. Accordingly, under Katz's method, the PTM and the PET are

not separate on a fragment, and the preferred peptide length of 5-12 amino acids would create significant problems for binding of a second antibody, as the capture antibody occupies most or all of the only available epitope on such a small peptide. Gembitsky fails to describe any step of fragmenting proteins and therefore fails to speak to this element of Applicants' claimed invention.

Neither Katz nor Gembitsky describe generating a capture agent that specifically binds a PET on a fragment separate from a PTM on the fragment, as required by the presently amended claims of the present invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

In addition, Applicants respectfully submit that the Office Action's suggestion to modify Katz in accordance with Gembitsky to find obviousness is in contradiction with current law in that it changes the essential function of the method described in Katz and renders the Katz method unsatisfactory for its intended purpose. Specifically, in its recent decision on *KSR Int'l. Co. v. Teleflex, Inc.*, the Supreme Court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a) and reiterated that a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Citing* Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U. S. 147, 152 (1950). Moreover, it is well accepted that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Assuming, for arguments sake, that a person with ordinary skill in the art tried to modify Katz as suggested by the Office Action, he would be required to take at least the following paradigmatic leaps to change the essential function of Katz's methods. First, he would be required to modify Katz's method to identify and include in the peptide selection the location of PTMs on examined polypeptides. This also would require including in the selected pool of peptides, many peptides containing the same type of PTM, for example, tyrosine phosphorylation sites. He would need to change essentially the function of Katz's method to

include this step. While Katz does suggest several parameters to consider for peptide selection, including molecular weight, amino acid composition, hydrophobicity, charge, secondary structure, heterogeneity, length, post-translational modifications, polarity, solubility, amphipathic nature, sequence, and immunogenicity, (Paragraph 76), the function of Katz's method is to provide a novel approach for producing peptides representative of polypeptides that, in part, are minimally cross- reactive. Paragraph 58. However, if the artisan includes many peptides containing the same type of PTM, capture agents directed to this same PTM will result in peptides that are highly cross-reactive.

Next, he would be required to analyze separated sequences in each Katz peptide. One portion would need to include a PTM, and another portion would need to include a PET or other indicia for identifying each particular peptide. He would need to change essentially the function of Katz's method to include this step. Specifically, the Katz specification does not teach or suggest breaking down its peptides into subcomponent parts before analyzing them. Rather, Katz indicates analyzing each of the peptide products, not separate and distinct parts of the peptide products. Paragraphs 77-78.

In addition, he would be required to generate more than one capture agent for each peptide. One capture agent would need to be directed against a PTM, and the other capture agent would need to be directed against a PET on the peptide. He would need to change essentially the function of Katz's method to include this step. Specifically, to create antibodies to two separate portions of Katz's peptides, he would likely be required to extend the length of Katz's peptides beyond Katz's preferred length of 5-12 amino acids. Paragraph 94. This alteration to Katz's method is in direct contradiction to the teaching of Katz and, according to Katz's own specification, undermines the function of Katz's method. Paragraph 94.

For at least these reasons, Applicants respectfully submit that modifying Katz's method in accordance with Gembitsky in the fashion suggested by the Office Action requires essential changes to the function of Katz's method, which conflicts with the recent Supreme Court ruling in *KSR Int'l. Co.* and with established precedent in *In re Gordon.*

Accordingly, because neither Katz nor Gembitsky, alone or in combination, teach or suggest at least the above-identified elements of the claims, as amended, of the present invention,

and because modification of Katz as described in the Office Action compromises the essential function of Katz's method, and therefore contradicts established precedent, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103(a) over Katz in view of Gembitsky further in view of Whaley

Claims 1 and 4-6 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Katz in view of Gembitsky further in view of Whaley *et al.* (1991) Biological Mass Spectrometry 20: 210-214 ("Whaley"). Applicants respectfully traverse this rejection to the extent that it is maintained over these claims in view of the following remarks.

Page 9, fourth paragraph, of the Office Action indicates that Whaley is being applied to Katz and Gembitsky to satisfy the limitation of Nearest-Neighbor Analysis, as required in dependent claims 4-6 of the present invention. Applicant has amended claim 4 to make clear that the Nearest Neighbor Analysis, as disclosed in the specification, is an amino acid sequence analysis, and therefore very different from the process described by the Whaley reference with the same name. Note further, claims 4-6 depend from and thus incorporate all the limitations of independent claim 1, as presently amended. For the reasons stated above, Applicants submit that neither Katz nor Gembitsky, alone or in combination, teach or suggest at least the above-identified elements of claims 4-6 as they depend from claim 1 of the present invention, and that modification of Katz using Gembitsky, as described in the Office Action, compromises the essential function of Katz's method, and therefore contradicts with established precedent. Further, Applicants submit that the addition of Whaley to Katz and/or Gembitsky fails to make up for the deficiencies in Katz and Gembitsky, alone or in combination.

In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

Applicants believe that, in the view of the above amendments and responses, the pending claims are in condition for allowance. Early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

Date: May 8, 2007

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